Clinical significance of preoperative fibre-tracking to preserve the affected pyramidal tracts during resection of brain tumours in patients with preoperative motor weakness

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Objective: To clarify the clinical usefulness of preoperative fibre-tracking in affected pyramidal tracts for intraoperative monitoring during the removal of brain tumours from patients with motor weakness.

Methods: We operated on 10 patients with mild to moderate motor weakness caused by brain tumours located near the pyramidal tracts under local anaesthesia. Before surgery, we performed fibre-tracking imaging of the pyramidal tracts and then transferred this information to the neuronavigation system. During removal of the tumour, motor function was evaluated with motor evoked potentials elicited by cortical/subcortical electrical stimulation and with voluntary movement.

Results: In eight patients, the locations of the pyramidal tracts were estimated preoperatively by fibre-tracking; motor evoked potentials were elicited on the motor cortex and subcortex close to the predicted pyramidal tracts. In the remaining two patients, in which fibre-tracking of the pyramidal tracts revealed their disruption surrounding the tumour, cortical/subcortical electrical stimulation did not elicit responses clinically sufficient to monitor motor function. In all cases, voluntary movement with mild to moderate motor weakness was extensively evaluated during surgery and was successfully preserved postoperatively with appropriate tumour resection.

Conclusions: Preoperative fibre-tracking could predict the clinical usefulness of intraoperative electrical stimulation of the motor cortex and subcortical fibres (ie, pyramidal tracts) to preserve affected motor function during removal of brain tumours. In patients for whom fibre-tracking failed preoperatively, awake surgery is more appropriate to evaluate and preserve moderately impaired muscle strength.

A number of anatomo-functional evaluations of the pyramidal tracts have been developed to help preserve motor function while maximising the removal of brain tumours located in close proximity to the pyramidal tracts. Integrated functional neuronavigation and preoperative neuroimaging, such as functional MRI (fMRI), magnetoencephalography (MEG) and fibre-tracking, have been combined with intraoperative electrical stimulation to establish the clinical significance of the findings of each evaluation method.^{1–6} Despite these developments in mapping and monitoring techniques, little is known about their clinical utility for patients suffering from motor weakness caused by brain tumours. As the tolerance of affected pyramidal tracts for surgical manipulation is weaker in comparison with that in patients without motor weakness, intraoperative evaluation plays a critical role in the surgeon's ability to maintain motor function. Decreased motor function itself, however, may affect the accuracy of intraoperative evaluation.

White matter fibre-tracking using diffusion tensor imaging is capable of visualising the integrity of white matter.^{1 4 7–11} Although fibre-tracking of the pyramidal tracts does not always correlate with the degree of motor weakness, it does reflect the functional condition of the fibres.¹⁶ To predict the clinical usefulness of intraoperative evaluation by presurgical non-invasive fibre-tracking imaging in patients with motor weakness, we compared the results of pyramidal tract fibre-tracking with the results of intraoperative direct electrical stimulation of the motor cortex and subcortical fibres (ie, pyramidal tracts) and spontaneous movements.

PATIENTS AND METHODS

Patients

We examined 10 patients, aged 28–67 years, who suffered from mild to moderate preoperative motor weakness due to brain tumours located close to the pyramidal tracts (table 1). The tumours included five cases of glioblastoma multiforme, three of anaplastic astrocytoma, one of diffuse astrocytoma and one cavernoma. All lesions were located within the language dominant frontal lobe; before operation, five patients had mild motor aphasia. In response to stimulation of the bilateral median and tibial nerves, scalp somatosensory evoked potentials (SEPs) were recorded in all patients. To evaluate cortical activity during voluntary movement, we evaluated finger/foot tapping during fMRI and MEG studies.

MRI data acquisition and diffusion tensor imaging (DTI) data processing for fibre-tracking and fibre-tractography reconstruction

Detailed methods for fibre-tracking have been described elsewhere.^{6 13} Preoperative DTI and anatomical T1/T2 weighted volume imaging used a 3 T MR scanner (Trio; Siemens, Erlangen, Germany). T1 weighted volume data were obtained using a three dimensional magnetisation prepared rapid gradient echo (MPRAGE) sequence. T2 weighted volume data

Abbreviations: DTI, diffusion tensor imaging; fMRI, functional MRI; MEG, magnetoencephalography; MEP, motor evoked potential; MPRAGE, magnetisation prepared rapid gradient echo; ROI, region of interest; SEP, somatosensory evoked potential

Table 1 Clinical characteristics of the 10 patients

Patient No	Age (y)	Sex	Histological type	Location
1	67	M	Glioblastoma multiforme	Left fronto-parietal
2	58	F	Glioblastoma multiforme	Left fronto-insulo-temporo-parietal
3	53	M	Anaplastic astrocytoma	Left fronto-parietal
4	28	M	Glioblastoma multiforme	Left fronto-parietal
5	40	F	Glioblastoma multiforme	Left frontal
6	40	F	Cavernoma	Left fronto-parietal
7	48	M	Diffuse astrocytoma	Left fronto-parietal
8	56	M	Anaplastic astrocytoma	Left frontal
9	60	F	Anaplastic astrocytoma	Left fronto-insulo-temporal
10	50	M	Glioblastoma multiforme	Right fronto-parietal

were obtained using a three dimensional true fast imaging with steady precession sequence. DtiStudio software was used to perform fibre-tractography based on the fibre-assignment by continuous tracking method.^{9–14} Fibre-tracking was initiated in both retrograde and orthograde directions according to the direction of the principal eigenvector in each voxel. Results that penetrated the manually segmented regions of interest (ROIs) were assigned to specific tracts. To reconstruct the pyramidal tract, two ROIs were segmented on axial $b = 0$ images: the first ROI at the cerebral peduncles and the second ROI at the precentral gyri.^{9–15–16} If the pyramidal tracts were not detected between the two ROIs because of the presence of tumours, the hyperintensity area at the internal capsule on the $b = 0$ image was selected as the second ROI.¹¹

Fibre-tractography data processing for navigation system

To convert tractography into a DICOM format dataset, three processing steps were applied. The first step was to change tractography to a voxel dataset. An 8 bit voxel dataset with binary contrast was created from the original tractography using DtiStudio, with the same matrix size as $b = 0$ images. In this voxelised tractography, marked voxels where fibre-tracts penetrate displayed the largest value, and other voxels the smallest ones.¹⁵ The second step was to create merged images of tractography and $b = 0$ images with the same matrix size as the MPRAGE images. The 3-orthogonal coordinates of each voxel in MPRAGE and $b = 0$ images were obtained from the DICOM header information. Trilinear interpolation was applied for

voxel value calculation. Merged images were generated from interpolated tractography and interpolated $b = 0$ images. The third step was to convert merged images into DICOM format, according to the MPRAGE header information. DICOM format tractography with the same imaging matrices as MPRAGE were obtained.

Preparation in the navigation system

The MPRAGE images, fast imaging with steady precession images and DICOM format tractography images were transferred to the navigation system (StealthStation TRIA plus, Medtronic Sofamor-Danek, Memphis, Tennessee, USA; or Vector Vision Compact Navigation System, Brain LAB AG Heimstetten, Germany) using Cranial 4.0/VV Cranial 7.5 software. We then applied non-rigid image fusion based on a mutual information algorithm using ImMerge/iPlan2.5 software. The day before the operation, we performed axial whole brain CT with a contiguous slice thickness of 1 mm and six independent scalp point markers for anatomical registration. The CT dataset was also input into the navigation system. CT, MPRAGE and DICOM format tractography were automatically registered; the anatomical registration points were verified to minimise navigation errors. As the differences in distortion between DTI and MPRAGE were within a few millimetres according to a phantom for the neuronavigation system, we determined that the spatial accuracy of the single shot echo planar sequence would be reliable; the potential error of the navigation due to image distortions would be limited to a few millimetres. At navigation setup, the accuracy of image registration was less than 2 mm. Fibre-tracking tractography

Table 2 Results of evaluation of motor function by preoperative and intraoperative assessments

Patient No	Motor weakness	MEG	fMRI	Scalp SEP	Fibre-tracking	MEPs (cortex)	MEPs (subcortex)	Awake surgery
1	Hand 4/5	x	x	x	x	o (unstable)	x	o
	Bracjium 3/5	x	x	x	x	x	x	o
	Leg 2/5	x	x	x	x	x	x	o
2	Hand, bracijum 1/5	x	x	x	x	x	x	o
	Leg 4/5	x	x	x	x	x	o (<1 cm)	o
3	Hand, bracijum 3/5	o	o	o	o	o	o (<1 cm)	o
4	Hand 4/5	o	o	o	o	o	o (<1 cm)	o
5	Hand 4/5	NA	NA	o	o	o	o (<1 cm)	o
6	Hand 4/5	o	o	o	o	o	o (<1 cm)	o
7	Hand, bracijum 4/5	NA	o	o	o	o	o (<1)	o
8	Hand 4/5	NA	NA	o	o	o	x (>2 cm)	o
9	Hand 4/5	o	NA	o	o	o	x (1 cm<<2 cm)	o
	Hand 4/5	NA	o	o	o	o	x (1 cm<<2 cm)	o

fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MEP, motor evoked potential; NA, not available; o, motor function detected; SEP, somatosensory evoked potentials; x, motor function was undetected. The distances between points of subcortical stimulation and the fibre-tracking pyramidal tracts are shown as less than 1 cm (<1 cm), between 1 and 2 cm (1 cm<<2 cm) or more than 2 cm (>2 cm).

Figure 1 Upper: preoperative T2 weighted MRI in patient Nos 3, 5, 6, 7, 8, 9 and 10, with brain tumours showing a hyperintense area that is close to the pyramidal tracts (red), identified by fibre-tracking. Lower: postoperative T2 weighted MRI demonstrated the extent of tumour removal. Postoperative fibre-tracking in patient Nos 3, 6 and 9 revealed preservation of the pyramidal tracts (red).

of the pyramidal tracts between the cerebral peduncle and the precentral gyrus was successful in 50 surgically treated brain tumour patients without motor weakness (data not shown).

Intraoperative electrical stimulation

The bilateral abductor pollicis brevis, biceps brachialis, deltoid, gastrocnemius, quadriceps femoris and tibialis anterior muscles were chosen for electromyogram recording using neurological monitoring (Epoch XP, Axon Systems, New York, USA). After induction, general anaesthesia was maintained by intravenous infusion with propofol for craniotomy. Muscle relaxants were administered only for intubation and were not continued during surgery. The highest N20–P20 phase reversal of cortical

SEPs was recorded using 4×5 subdural electrodes to identify the central sulcus. If SEPs were not sufficient to define the central sulcus, intraoperative visual inspection of the sulci combined with neuronavigation was used to orient the anatomy. After discontinuing the propofol infusion, patients awoke without further deficits.

To monitor motor function of the corticospinal tracts electrophysiologically, we first stimulated the precentral gyrus to identify a positive control motor evoked potential (MEP) and the intensity appropriate to stimulate subcortical fibres. The intensity of cortical stimulation was increased from 5 mA to a maximum of 25 mA. If afterdischarges were induced, we repeated the test at the same intensity or using a 1 mA lower

Figure 2 Patient No 4 had a left fronto-parietal glioblastoma multiforme. (A) Preoperative fibre-tracking identified symmetrical pyramidal tracts (red lines) from the cortex to the cerebral peduncles. (B) Brain T2 weighted MRI revealed a hyperintense area in close proximity to the left pyramidal tract, identified by fibre-tracking (red). Cortical stimulation of the left precentral gyrus, which had been defined by a somatosensory evoked potential, elicited a motor evoked potential (MEP) in the right abductor pollicis brevis muscle (Cortex). During removal of the tumour, subcortical stimulation elicited MEPs at the bottom of the tumour (intersection of the yellow lines in the intraoperative navigation image), 1 cm from the edge of the predicted pyramidal tract (red) (Subcortex). To avoid causing additional neurological deficits, no further removal was performed. (C) Postoperative T2 weighted MRI demonstrated preservation of the pyramidal tracts identified by fibre-tracking (red).

Figure 3 Patient No 1. Fibre-tracking of the pyramidal tracts was disrupted in a 67-year-old man with a left fronto-parietal glioblastoma multiforme. Upper: preoperative T2 weighted MRI identified a focus of hyperintensity in the left perirolandic region with gadolinium enhancement of the rostral precentral cortex. Stimulation of the left cortex rarely elicited weak motor evoked potential (MEP) responses on the right abductor pollicis brevis muscle. Subcortical stimuli, even on the approximated posterior bank of the precentral gyrus on neuronavigation (intersection of the yellow lines in the intraoperative navigation image), did not elicit MEPs. Middle: a relative anisotropy map indicated the principal eigenvector (green, anterior–posterior; red, right–left; and blue, inferior–superior). Fibre-tracking of the left pyramidal tracts (red lines) near the tumour was disrupted during its course to the cortex. Lower: postoperative MRI with gadolinium enhancement.

current. During removal of tumour tissue within 2 cm of the pyramidal tracts by intraoperative neuronavigation, we performed repetitive subcortical electrical stimulations. Electrical stimuli were applied across a relatively wide area to avoid any anatomical shift caused by the tumour. Five trains of monophasic square waves with a duration of 0.2 ms were applied. Current was delivered by a pair of adjacent electrodes (3 mm in diameter) with a centre-to-centre inter-electrode distance of 1 cm.³ A 50 Hz electric current was delivered for language and sensory testing. Language functions were assessed by the reading of a paragraph, spontaneous speech, naming and comprehension activities.¹⁷ We confirmed the points of stimulation by visualisation using the navigation system. In all patients, the minimum distances between points of stimulation and the fibre-tracking pyramidal tracts were measured using three dimensional MRI by intraoperative neuronavigation.

Surgery

All patients underwent removal of their tumour under local anaesthesia using the combination of tractography integrated functional neuronavigation and direct cortical/subcortical stimulation. During removal of the tumours around the pyramidal tracts, motor function of all four extremities was continuously monitored using the muscle manoeuvre test.¹⁸ Language

function was evaluated using similar testing as that used for electrical stimulation, depending on the location of the tumour. In three patients in whom part of the tumour extended into the left angular gyrus, single digit multiplication was evaluated. All procedures were approved by the ethics committee (No 542); written informed consent was obtained from all patients. As the presence of subcortical MEPs during resection of the tumour is an important sign warning of permanent motor weakness, we avoided further resection after obtaining the first MEP response.^{19 20}

RESULTS

Results of evaluation of motor function by preoperative and intraoperative assessments are summarised in table 2. Preoperative fibre-tracking identified the pyramidal tracts of eight patients, including seven with mild hand motor weakness (patient Nos 4–10) and one with moderate motor weakness (3/5) of his upper limb (patient No 3) (figs 1, 2). In all patients, MEPs were elicited for all of the muscles evaluated, including the weakened muscles, by electrical stimulation of both the precentral gyrus and the subcortex within 1 cm of the pyramidal tracts, identified by intraoperative functional neuronavigation. The tumours were removed while confirming stable MEP responses by repetitive electrical stimulation. Motor function was either

Figure 4 Patient No 2. Left: fibre-tracking of the pyramidal tracts (red lines) demonstrated disruption around a left fronto-insulo-temporo-parietal glioblastoma multiforme. Middle: during removal of the tumour, cortical stimuli did not elicit any motor evoked potentials (MEPs). Subcortical stimuli very close to the predicted pyramidal tracts (red) on neuronavigation (intersection of the yellow lines in an intraoperative navigation image), however, elicited MEPs of her affected right lower extremities, but not her right upper extremities. Right: Postoperative T2 weighted MRI demonstrated that the pyramidal tracts identified by fibre-tracking (red) were preserved.

maintained or improved both during and after the operation. In addition, we demonstrated preservation of the pyramidal tracts by postoperative fibre-tracking (patient Nos 3, 4, 6 and 9).

In two patients (patient Nos 1 and 2), fibre-tracking of the pyramidal tracts around the tumour failed. Patient No 1 (fig 3) suffered from preoperative right hemiparesis (3/5 on the brachium, 4/5 on the hand and 2/5 on the leg) because of left fronto-parietal glioblastoma multiforme. Cortical SEPs exhibited weak responses on stimulation of the right median nerve; no response was observed after stimulation of the right tibial and sural nerves. Cortical stimulation of the anatomically confirmed precentral gyrus by neuronavigation elicited a rare MEP in his abductor pollicis brevis muscle; no MEPs were elicited in his biceps brachialis, deltoid, gastrocnemius, quadriceps femoris or tibialis anterior muscles. Neurological examinations soon after the patient recovered from general anaesthesia demonstrated no additional deficits. As the tumour was removed piece by piece, continuous evaluation of muscle strength helped preserve motor function of the lower extremities and improve motor function of the upper extremities to 4/5. Subcortical electrical stimulation did not elicit MEPs at any point during resection of the tumour. Patient No 2 (fig 4) exhibited right hemiparesis (1/5 on the upper extremity and 4/5 on the leg) preoperatively, caused by a left fronto-insulo-temporo-parietal glioblastoma multiforme. We operated on this patient with the goal of preserving motor function of the lower extremities. She also displayed mild motor aphasia. Cortical SEPs could not be elicited. Despite the absence of MEP responses following cortical stimulation of the wide area surrounding the anatomically identified precentral gyrus by neuronavigation, subcortical stimulation elicited MEPs of her lower but not upper extremities. Through continuous evaluation of muscle strength intraoperatively, motor function of the lower extremities was preserved during removal of the tumour. Postoperatively, she exhibited adequate removal of the tumour without any further neurological deficits.

DISCUSSION

To maintain the quality of life of patients with motor weakness undergoing surgical treatment of brain tumours, it is essential to evaluate motor function intraoperatively. The damage done to the pyramidal tracts, however, may affect the results of the evaluation. As MEPs elicited by direct intraoperative electrical stimulation remain the most reliable index of motor function,^{21–23} it is important to predict if MEP responses will be elicited from the affected motor cortex and the pyramidal tracts during removal of the tumour. Presurgical evaluations, such as the degree of motor weakness (muscle strength), MEG, fMRI, positron emission tomography, transcranial magnetic stimulation and fibre-tracking

are all potential candidates for predicting intraoperative MEP responses.

In this study, the degree of preoperative motor weakness did not always correlate with the incidence of intraoperative MEP responses. Muscles that were moderately affected by compression caused by the tumour elicited MEPs following cortical/subcortical stimulation (patient No 3), a result that is consistent with previous case reports.^{2–24} MEP responses, however, could not be elicited from only mildly affected muscles in two patients (patient Nos 1 and 2). MEG, fMRI and positron emission tomography images provide information concerning motor function at the cortical, but not subcortical, level. Repetitive voluntary movements are often necessary to elicit motor evoked fields by MEG and bold effects by fMRI. While preoperative scalp SEPs correlated with the incidence of MEP responses in our patients, the results of SEP assessments do not directly reflect motor function.

Fibre-tracking of the affected pyramidal tracts was first compared with the incidence of intraoperative MEP responses by direct cortical/subcortical electrical stimulation. Subcortical MEPs were always elicited in regions in close proximity to the pyramidal tracts that had been predicted by fibre-tracking in patients with mild to moderate preoperative motor weakness. In addition, continuous fibre-tracking of the pyramidal tracts from the motor cortex to the cerebral peduncle indicated the positive response of cortical MEPs. On the other hand, cortical MEPs were never elicited as reliable responses in patients with disrupted fibre-tracking pyramidal tracts. These data suggest that preoperative fibre-tracking of the pyramidal tracts provides anatomical information as well as functional information in predicting the clinical usefulness of intraoperative cortical/subcortical electrical stimulation.

Several limitations to fibre-tracking as a preoperative evaluation, however, should be mentioned. Selection of the seed ROIs and the thresholding of fractional anisotropy, which define the parameter of the algorithm used in the procedure, may subjectively affect the errors in track trajectories.^{8–25–26} In the present study, individual muscle maintained various degrees of motor activity preoperatively instead of disruption on the fibre-tracking pyramidal tracts, which may reflect the limitations of fibre-tracking from technical errors and pathological conditions. Part of the pyramidal fibres tracking from the precentral gyrus in lower convexity may fail to trace the precise course because the pyramidal tract intersects with callosal fibres and the superior longitudinal fasciculus at the level of the centrum semiovale.^{3–27–28} Lack of visualisation of some upper limb fibres would account for some of the discrepancies between extent of weakness and ability to visualise fibres. To compare the pyramidal fibres tracking and MEP responses more precisely, taking intraoperative brain shift²⁹

into consideration, DTI image processing during the course of surgery with the use of intraoperative MRI is needed.^{5 30 31} In addition, individual pathophysiological factors resulting from the brain tumours may affect the results of fibre-tracking,^{2 10 20 32 33} although it is controversial whether the tumour itself or peritumoral oedema on the pyramidal tracts can be distinguished by DTI metrics.^{34 35} In the two such patients evaluated in this study, preservation of motor function indicated that secondary effects, such as oedema or mass effect, rather than tumour infiltration, caused the motor deficits. Relatively large amounts of peritumoral oedema in these patients compared with the other eight patients might cause unsuccessful fibre-tracking of the pyramidal tracts. Although a wide area was stimulated electrically, a portion of the pyramidal tracts may have been shifted by compression of the tumour. Further studies with a larger number of patients will be necessary to study the physiological significance of fibre-tracking of affected pyramidal tracts and to clarify the clinical relationship between preoperative fibre-tracking and intraoperative cortical/subcortical electrical stimulation. The tendency for patients not to be operated on until they begin to suffer from moderate motor weakness due to growing brain tumours may, however, limit these studies. In addition, post-operative fibre-tracking of the pyramidal tracts and neurological status should be compared with the extent of tumour resection for further verification of the clinical value of preoperative fibre-tracking.

Despite the clinical utility of complete pyramidal tract fibre-tracking in reliable MEPs of the motor cortex and pyramidal tracts, disruption of estimated pyramidal tracts suggested that electrical stimulation is insufficient to permit the preservation of motor function during tumour removal. For patients with mild to moderate motor weakness in whom pyramidal tract fibre-tracking failed preoperatively, awake surgery would be better suited to evaluate motor function by voluntary movement during removal of the tumour. As awake surgery allows spontaneous movements to be easily monitored continuously, it would be useful for a subset of pathological conditions.³⁶ During removal of a tumour under local anaesthesia, injuries to motor associated areas must also be considered. Motor weakness is not observed immediately after resection of the supplementary motor area³⁷ whereas an injury to the negative motor area after resection would cause an immediate and transient disturbance in fine movement.¹⁷

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